

Claims

1. (currently amended) A heterologous fusion protein comprising
a GLP-1 analog of SEQ ID NO:1

His-~~Xaa₈~~Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu-
Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Gly-Gly
~~wherein Xaa₈ is Gly;~~

~~an fused to the~~ Fc portion of an immunoglobulin of SEQ ID NO:7

Ala-Glu-Ser-Lys-Tyr-Gly-Pro-Pro-Cys-Pro-Pro-Cys-Pro-Ala-Pro-
~~Xaa₁₆~~Glu-~~Xaa₁₇~~Ala-~~Xaa₁₈~~Ala-Gly-Gly-Pro-Ser-Val-Phe-Leu-Phe-Pro-Pro-
Lys-Pro-
Lys-Asp-Thr-Leu-Met-Ile-Ser-Arg-Thr-Pro-Glu-Val-Thr-Cys-Val-
Val-Val-Asp-Val-Ser-Gln-Glu-Asp-Pro-Glu-Val-Gln-Phe-Asn-Trp-
Tyr-Val-Asp-Gly-Val-Glu-Val-His-Asn-Ala-Lys-Thr-Lys-Pro-Arg-
Glu-Glu-Gln-Phe-~~Xaa₈₀~~Asn-Ser-Thr-Tyr-Arg-Val-Val-Ser-Val-Leu-Thr-
Val-Leu-His-Gln-Asp-Trp-Leu-Asn-Gly-Lys-Glu-Tyr-Lys-Cys-Lys-
Val-Ser-Asn-Lys-Gly-Leu-Pro-Ser-Ser-Ile-Glu-Lys-Thr-Ile-Ser-
Lys-Ala-Lys-Gly-Gln-Pro-Arg-Glu-Pro-Gln-Val-Tyr-Thr-Leu-Pro-
Pro-Ser-Gln-Glu-Glu-Met-Thr-Lys-Asn-Gln-Val-Ser-Leu-Thr-Cys-
Leu-Val-Lys-Gly-Phe-Tyr-Pro-Ser-Asp-Ile-Ala-Val-Glu-Trp-Glu-
Ser-Asn-Gly-Gln-Pro-Glu-Asn-Asn-Tyr-Lys-Thr-Thr-Pro-Pro-Val-
Leu-Asp-Ser-Asp-Gly-Ser-Phe-Phe-Leu-Tyr-Ser-Arg-Leu-Thr-Val-
Asp-Lys-Ser-Arg-Trp-Gln-Glu-Gly-Asn-Val-Phe-Ser-Cys-Ser-Val-
Met-His-Glu-Ala-Leu-His-Asn-His-Tyr-Thr-Gln-Lys-Ser-Leu-Ser-
Leu-Ser-Leu-Gly-Xaa₂₃₀

wherein:

~~Xaa at position 16 is Glu;~~

~~Xaa at position 17 is Ala;~~

~~Xaa at position 18 is Ala;~~

~~Xaa at position 80 is Asn; and~~

Xaa at position 230 is Lys or is absent;

and further comprising a peptide linker of SEQ ID NO:8

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Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Ser

wherein the N-terminal glycine of the peptide linker is directly fused to ~~between the~~
C-terminal glycine residue of the GLP-1 analog and the C-terminal serine of the
peptide linker is directly fused to N-terminal alanine of the Fc portion.

2.-15. (cancelled)

16. (currently amended) A method of treating a patient with non-insulin dependent diabetes mellitus comprising the administration of a therapeutically effective amount of the heterologous fusion protein of any one of Claims ~~1 to 8~~ 30 to 34.

17. (currently amended) A method of inducing weight loss in an overweight patient comprising the administrations of a therapeutically effective amount of the heterologous fusion protein of any one of any one of Claims ~~1 to 8~~ 30 to 34.

18.-25. (cancelled)

26. (currently amended) A The heterologous fusion protein of Claim 1 wherein
comprising

~~a GLP-1 analog of SEQ ID NO:1~~

~~His Xaa₈ Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu Gln
Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Gly Gly
wherein Xaa₈ is Gly;~~

~~fused to the Fc portion of an immunoglobulin of SEQ ID NO:7~~

~~Ala Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
Xaa₁₆ Xaa₁₇ Xaa₁₈ Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
Glu Glu Gln Phe Xaa₃₀ Ser Thr Tyr Arg Val Val Ser Val Leu Thr
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys~~

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~~Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val
Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
Leu Ser Leu Gly Xaa₂₃₀~~

wherein:

~~Xaa at position 16 is Glu;~~

~~Xaa at position 17 is Ala;~~

~~Xaa at position 18 is Ala;~~

~~Xaa at position 80 is Asn; and~~

~~Xaa at position 230 is absent;~~

~~and further comprising further comprising a peptide linker of SEQ ID NO:8~~

~~Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser~~

~~wherein the peptide linker is between the C-terminal glycine residue of the GLP-1
analog and the N-terminal alanine of the Fc portion.~~

27. (new) A heterologous fusion protein whose amino acid sequence consists of
a GLP-1 analog of SEQ ID NO:1

~~His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu-Gln-
Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Gly-Gly;~~

~~an Fc portion of an immunoglobulin of SEQ ID NO:7~~

~~Ala-Glu-Ser-Lys-Tyr-Gly-Pro-Pro-Cys-Pro-Pro-Cys-Pro-Ala-Pro-
Glu-Ala-Ala-Gly-Gly-Pro-Ser-Val-Phe-Leu-Phe-Pro-Pro-Lys-Pro-
Lys-Asp-Thr-Leu-Met-Ile-Ser-Arg-Thr-Pro-Glu-Val-Thr-Cys-Val-
Val-Val-Asp-Val-Ser-Gln-Glu-Asp-Pro-Glu-Val-Gln-Phe-Asn-Trp-
Tyr-Val-Asp-Gly-Val-Glu-Val-His-Asn-Ala-Lys-Thr-Lys-Pro-Arg-
Glu-Glu-Gln-Phe-Asn-Ser-Thr-Tyr-Arg-Val-Val-Ser-Val-Leu-Thr-
Val-Leu-His-Gln-Asp-Trp-Leu-Asn-Gly-Lys-Glu-Tyr-Lys-Cys-Lys-
Val-Ser-Asn-Lys-Gly-Leu-Pro-Ser-Ser-Ile-Glu-Lys-Thr-Ile-Ser-
Lys-Ala-Lys-Gly-Gln-Pro-Arg-Glu-Pro-Gln-Val-Tyr-Thr-Leu-Pro-
Pro-Ser-Gln-Glu-Glu-Met-Thr-Lys-Asn-Gln-Val-Ser-Leu-Thr-Cys-
Leu-Val-Lys-Gly-Phe-Tyr-Pro-Ser-Asp-Ile-Ala-Val-Glu-Trp-Glu-~~

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Ser-Asn-Gly-Gln-Pro-Glu-Asn-Asn-Tyr-Lys-Thr-Thr-Pro-Pro-Val-
Leu-Asp-Ser-Asp-Gly-Ser-Phe-Phe-Leu-Tyr-Ser-Arg-Leu-Thr-Val-
Asp-Lys-Ser-Arg-Trp-Gln-Glu-Gly-Asn-Val-Phe-Ser-Cys-Ser-Val-
Met-His-Glu-Ala-Leu-His-Asn-His-Tyr-Thr-Gln-Lys-Ser-Leu-Ser-
Leu-Ser-Leu-Gly-Xaa₂₃₀

wherein Xaa at position 230 is Lys or is absent;

and a peptide linker of SEQ ID NO:8

Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser

wherein the N-terminal glycine of the peptide linker is directly fused to the C-terminal glycine residue of the GLP-1 analog and the C-terminal serine of the peptide linker is directly fused to N-terminal alanine of the Fc portion.

28. (new) The heterologous fusion protein of Claim 27 wherein Xaa at position 230 is absent.
29. (new) The heterologous fusion protein of Claim 28 wherein the fusion protein is encoded by the DNA of SEQ ID NO:20.
30. (new) The heterologous fusion protein of claim 1 wherein the fusion protein is glycosylated.
31. (new) The heterologous fusion protein of claim 26 wherein the fusion protein is glycosylated.
32. (new) The heterologous fusion protein of claim 27 wherein the fusion protein is glycosylated.
33. (new) The heterologous fusion protein of claim 28 wherein the fusion protein is glycosylated.
34. (new) The heterologous fusion protein of claim 29 wherein the fusion protein is glycosylated.